A NEW GOLD STANDARD FOR SYPHILIS?

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ABSTRACT

Novel PCR screening on whole blood has found *T. pallidum* DNA in erythrocytes of young gay men in Budapest who are repeatedly negative in all other standard syphilis tests, including treponemal antibody screening (TPHA). This follows on historical evidence suggesting syphilis has been under-diagnosed ever since screening with non-specific anti-lipoidal antigens began in 1906.

The first half of the 20th century saw the development of complement fixation and precipitation/flocculation assays, which were often used together to increase sensitivity and specificity, because many cases proved difficult. Syphilis sequelae often occurred despite lifelong negative anti-lipoidal serology.

The arrival of treponemal tests (TPI in 1949) further increased the sensitivity, and also excluded many false positives, although this class of test lacked sensitivity in primary syphilis. Vienna's teaching hospitals have also confirmed over many years that the TPHA finds nearly twice as many undetected cases as the VDRL. The avidity/affinity index as a surrogate for IgM antibody (Boltzmann Institute for Serodiagnosis, Vienna) found many active cases with no VDRL reactions. Despite these refinements, Ontario's Public Health Laboratory has documented the selective loss of treponemal antibody among HIV antibody(+) gay men, making it difficult - if not impossible - to assess the

prevalence of syphilis.

Since the early 1990s, recombinant antigens have provided even greater sensitivity, confirmed again in Toronto by reactive immunoblots - both IgG and IgM - among men at high risk for syphilis. Yet these VDRL(-) and often TPHA (-) persons remain undiagnosed. Using the PCR in South Africa, the CDC's Multiplex assay has proven that the VDRL misses most primary syphilis when the DNA of other ulcerative STDs is present.

The increased sensitivity of newer tools will allow a better assessment of the true morbidity and mortality caused by syphilis, and suggests the gold standard for screening select populations will ultimately require gene amplification.

RETHINKING THE WASSERMANN TEST

Since the beginning of syphilis antibody screening in 1906, there have always been concerns about the sensitivity of the non-specific anti-lipoidal tests and their more recent variations, the RPR and VDRL. Before 1950, these non-specific tests, often named after their developers, were run together to increase sensitivity in suspected syphilis cases. (1) In the years just before WWII, these versions of the Wassermann technique were quantifiable, and the VDRL researchers worked to standardise these tests, leading to our current screening paradigm.

But all along assumptions were made - assumptions based on clinical acute cases - that these tests could almost always detect the disease, and sensitivity may have been sacrificed for the sake of this reproducibility. There was never a gold standard for latent syphilis, only these assumptions - a concern voiced by one of America's greatest syphilis authors in 1944. (2)

With the arrival in 1949 of the first reproducible treponemal antibody test (T. pallidum Immobilisation or TPI), (3) cases of latent syphilis could be verified without obvious symptoms or positive anti-lipoidal test results. This is why every subsequent summary of syphilis screening acknowledges much greater sensitivity for the treponemal tests (TPHA, FTA-Abs, TPI) in diagnosing the late latent stages.

Evidence from the syphilis animal models further demonstrates that detection by anti-lipoidal serology misses many or most cases of the disease:

- In the mouse model, many pre-1960 investigators, such as Paul Rosahn from Yale, and Europe's Levaditi & Kolle, proved undoubted silent syphilis infection without the standard anti-lipoidal reaction. The 100% absence of a VDRL reaction in the FTA-Abs(+) mouse model was confirmed again recently in Budapest. (4)

- In the rabbit model, the adapted Nichols laboratory strain of *T. pallidum* was manipulated specifically for its ability to reliably cause symptoms and seroconversion, as well as provide a source of antigen for research.

However, depending on the timing of re-exposure, rabbits could be demonstrably re-infected with the Nichols strain with no classical blood reaction. (5-7) As well, this model was unreliable for the serodiagnosis of syphilis following mucosal inoculation: intra-meatal, sub-preputial, oral, and intra-vaginal infection with the Nichols strain led very often to seronegative but proven systemic infection in this model. (8)

- In the primate model, J. Lawton Smith at the University of Miami studied the serology and morbidity of owl monkeys with ocular syphilis, and found that most were negative or equivocal in the VDRL after mucosal *T. pallidum* challenge, and only sometimes reactive in the FTA-Abs treponemal test. (9)

As a result of these inconsistencies in the animal test results (implying defective antigen processing), seronegative syphilis in humans could be a regular occurrence. Hence, investigators in the first half of the 20th century tried to establish a gold standard for the direct detection of *T. pallidum* in clinical specimens. In addition to darkfield and staining in ultrathin sections, the rabbit infectivity test (RIT) was helpful in often proving syphilis when suspected but not serologically or clinically confirmed. But RIT detects only virulent organisms, and hence was often negative in the presence of treponemes confirmed by darkfield microscopy, (8) and/or serologic testing. (10)

IMPROVING SYPHILIS DIAGNOSIS

These sensitivity concerns were well understood by some investigators as syphilis rates began to soar in the 1960s and 1970s. Screening with treponemal tests, including ELISA testing with recombinant *T. pallidum* antigens, has been undertaken in several centres. Two teaching hospitals in Vienna recently summed up 20 years of experience, concluding that, in the aggregate, treponemal screening with TPHA or MHA-Tp identified about twice as much syphilis as the VDRL. (11)

T. pallidum cannot be cultured in an artificial medium, which has proven to be a major problem in getting useful and affordable quantities of antigen for specific and sensitive tests, and for vaccine research as well. But with the use of the recombinant antigens, Toronto investigators have achieved greater sensitivity without losing specificity, finding otherwise undetected latent syphilis in at least five percent of specimens from at-risk male patients. (12) Most of these cases were unknown to public health authorities, were untreated, and were RPR(-) and TPHA(-).

Detection of primary syphilis can be just as problematic serologically, as nearly two-thirds of ulcerative STD containing T. pallidum DNA have been found to be seronegative in the RPR test when the DNA of other ulcerative STDs is also present in the lesions. (13)

As a result, one could conclude that the diagnosis of syphilis has become more and more a task for the laboratory - and less for the clinician - and a recent preliminary PCR screening effort on whole blood adds yet another level of sensitivity. (14)

A total of 105 gay males attending a dermatology practice in Budapest have all been screened with four tests: RPR, TPHA, HIV Elisa, and the whole blood syphilis nested PCR. Seven cases of syphilis (average age 26) were detected using syphilis PCR, but only two with a treponemal assay, the accepted standard for detecting latent syphilis. The results of all tests were as follows:

4 cases were PCR (+) TPHA (-) RPR (-) HIV (-)
1 case was PCR (+) TPHA (+) RPR (+) HIV (-)
1 case was PCR (+) TPHA (+) RPR (-) HIV (-)
1 case was PCR (+) TPHA (-) RPR (-) HIV (+)

Interestingly, the only HIV (+) case out of these 105 men was also syphilis PCR (+), as were the only two TPHA (+) treated cases. One of these TPHA (+) cases was the only reactor in the RPR test in the entire cohort, none of whom had signs or symptoms of early syphilis. The probability that these PCR results are a chance observation is very remote. Others have proven persistent syphilis using this technique. (15) The clinical implications of all these findings remain unknown.

DISCUSSION

It is disturbing to find so much unexpected syphilis every time a new experimental technique is introduced. But the fact may well be that syphilis prevalence has always been underestimated. Indeed, the greatest morbidity and mortality caused by syphilis may be going unaddressed by our current assumptions about diagnosis and treatment.

Many pre-penicillin authors speculated that excess mortality - reactivation tuberculosis, pneumonias, and cancers - could result from inadequately treated or untreated syphilis. (16-20) In the classical natural history studies, these complications were at least twice as prevalent as the classical late fatal sequelae. (21, 22)

It could also be argued that syphilis shortens the life of the mouse (23, 24) and owl monkey, (9, 25) but investigators did not understand what may have been going on when their experimental subjects wasted away and died prematurely. J. Earle Moore, editor of the American Journal of Syphilis, may have been quite right in asking in 1939 whether it was "justifiable to assume, as did Osler, that syphilis actually ranks first, instead of its apparent tenth, among killing infections?" (26)

It has been generally assumed that latent syphilis is inactive syphilis, as opposed to a chronic active process. However, Evan Thomas' 1949 summary of two thousand syphilitic cases in New York City (27) provides good clinical evidence that latent syphilis may indeed be very active from an immunological point of view, likely as a result of the development of tolerance/peripheral inhibition (i.e. immune deviation).

While there is resistance to syphilis in the early stages of the disease, it appears that, unless promptly treated, the host eventually loses the battle. After several

months, immune deviation silently develops over time in most untreated latent cases, making the disease much harder to detect and cure, especially in cases of re-infection. Evan Thomas concluded that after two years of untreated disease, there is a near-universal loss of the host's ability to respond to *T. pallidum* again, a state irreversible by therapy. If left untreated long enough, patients very rarely developed typical early signs or symptoms or reactive tests again upon re-exposure.

This non-responsiveness was once known as "syphilisation", (28) a concept developed following observations that after a few exposures, the classical symptoms were never seen again. Natural immunity (immunitas in Latin means "exemption from") does not exist in syphilis, and prior infection does not lead to protection against re-challenge. (29)

This absence of natural immunity was also apparent in the failed attempts to make a skin test for syphilis, despite success with many other immunogens as precedents: leishmanin, coccidiodin, histoplasmin, pneumocystin, blastomycosin, and tuberculin. All of these antigens could be made to work reliably, and provide evidence on the prevalence of exposure and natural immunity. Almost all healthy and exposed persons in endemic areas skin-tested with these antigens had the G & C type IV response, the indurated erythema. But luetin preparations from *T. pallidum* suspensions could not be manipulated to reliably produce this recall phenomenon.

These kinds of concerns have led many investigators to study the immunophenotypes of antigen processing cells in syphilis. (30-39) The available evidence suggests that syphilis, if not diagnosed and cured in its early stages, leads to global suppression of the Th1 immune response and the regulation of immunity towards the Th2 phenotype. (40-42)

Clinically, the work of authors 50 years ago suggested this phenomenon of immune regulation in human subjects. (43, 44) Tuberculin recall screening in late syphilitics at the University of Vienna showed most subjects had lifelong loss of TB recall, in distinct contrast to the regular hospital admissions. (45)

Looking at these concerns in our modern era of HIV/AIDS, millions of cases of syphilis seem to have disappeared among the very populations recently saturated with this old STD, (46-48) but who are now said to be dying of a "new" disease of immunodeficiency. Indeed, Houston syphilis author Daniel Musher has remarked that syphilis seems to have "melted away" in these at-risk populations. (49) Or has a reservoir of latent disease become invisible because of the syphilisation effect and the accompanying insensitive diagnostic paradigm?

CONCLUSION

Given all these unknowns in the diagnosis and treatment of syphilis, more basic research into the prevalence of the disease and its immunopathology is urgently required, especially within the context of our recent recognition of immunosuppression and HIV/AIDS:

- The widely-held assumption that most patients retain their treponemal antibody status following seropositive early syphilis needs to be revisited, in light of the Toronto experience of testing and treating HIV cases who had selectively lost their treponemal antibody response during the polyclonal B-cell activation of advancing HIV disease. (50-52)

- The specificity of our 47kDa-based PCR test (53) needs to be further confirmed, perhaps using genes for one of the *T. pallidum* enzymes. DNA isolation results then need to be quantified and evaluated to see whether there is a relationship with depressed cellular immunity. This relationship may well be largely independent of HIV status, as low T-cell levels have been found in populations with high syphilis rates, (54) and it is unclear what effect - if any - HIV has on the course of syphilis and the response to treatment. (55-56) More aggressive treatment may be needed to clear the treponemal DNA, given the problems achieving adequate serologic response by conventional criteria. (57)

- The primate syphilis model needs to be revisited, including within the HIV model, to confirm earlier findings suggesting global immune suppression due to unresolved syphilis. There may also be a more affordable model in the mouse, guinea pig or rabbit.

- There needs to be investigation of node biopsies from HIV and AIDS cases in whom a whole blood syphilis PCR is positive. The histology of lymph node changes in syphilis is remarkably similar to that seen in advancing HIV disease. (58)

- Clinicians worldwide need to re-screen all their patients - including those without HIV - for treponemal antibody, using recombinant tests, until revised guidelines are issued. These test results must be prospectively analysed for years alongside some type of nucleic acid amplification system, in order to establish whether antibody screening can identify all those infected with *T. pallidum*. Blood donor lots also need to be screened this way, as is done routinely in the case of HIV.

If syphilis detection is better managed through the use of a new gold standard, we may reduce not only the incidence and prevalence of syphilis, but also rates of HIV transmission and progression to AIDS. There may well be an immunological synergy between these two ancient infections that goes far beyond the already well-documented role of ulcerative STDs in HIV acquisition.

http://members.rogers.com/colman/eadv/

SOBERING QUOTES

"In spite of 400 years of study, we still do not know the actual importance of syphilis as a cause of death. To what extent does death directly from syphilis masquerade under other diagnoses: or to what extent is syphilis an indirect cause of death from other conditions? Is it justifiable to assume, as did Osler, that syphilis actually ranks first, instead of its apparent tenth, among killing infections?"

-J. Earle Moore, 1939 (26)

"Within 2 years after infection, untreated syphilis produces immune changes in the host which, with rare exceptions, are permanent and make it impossible for tissues to react to subsequent infection with development of early syphilitic lesions."

-Evan W. Thomas, 1949 (27)

"Far from eradicating syphilis, antibiotics are driving the disease underground and increasing the difficulty of detection. Although the incidence of disease has more than tripled since 1955, the chancre and secondary rash no longer are commonly seen. Undoubtedly, some of these lesions are being suppressed and the disease masked by the indiscriminate use of antibiotics. The ominous prospect of a widespread resurgence of the disease in its tertiary forms looms ahead."

-Armand J. Pereyra, 1970 (59)

"A substantial proportion of HIV-infected men may have unrecognized, latent, inadequately treated syphilis. These findings support more aggressive treatment of T. pallidum infection in this patient population."

-Daniel M. Musher, 1990 (60)

"The clinical manifestations of syphilis, which have taken various forms over the centuries, have now been transformed to mimic the appearance of the opportunistic infections and cancers that may accompany HIV infection, as well as the clinical symptoms of AIDS itself."

-Sandra A. Larsen, 1991 (61)

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